AR201-13783A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL PROPYL KETONE
(CAS NO.: 107-87-9)

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl propyl ketone (MPK; CAS NO.: 107-87-9) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data in conjunction with EPA-acceptable predictive computer models, and values from reputable textbooks to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that these data are completely adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl propyl ketone is a colorless liquid capable of being manufactured to a high degree of purity. It has been reported to occur in many fruits, trees and shrubs, and is released naturally to the environment as a plant volatile, as a product of combustion, via photooxidation, and from microbial degradation of other chemicals. The FDA has approved its use in food under 21CFR 172.515. Nevertheless, this solvent finds its primary function as a solvent in various coating applications, in the electronics industry, as well as a solvent in industrial cleaning solutions. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 200 ppm (705 mg/m^3).

TEST PLAN SUMMARY

CAS No. 107-87-9	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	Y	-	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained from a reputable textbook referenced in Hazardous Substances Data Base (HSDB).

Boiling Point - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Vapor Pressure - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Partition Coefficient - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Water Solubility - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Conclusion: All end points haven been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained from a manuscript referenced in HSDB.

Stability in Water - A technical discussion describing the stability of ketones in water was provided.

Biodegradation - This endpoint was satisfied through two studies. Both followed established guidelines and one was conducted under GLP assurances. (The other was conducted prior to the enactment of GLP.)

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1).

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Toxicity to Aquatic Plants - This endpoint is filled by data from a study that followed an established OECD guideline (#201) and was conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies. The algal study followed OECD guidelines and GLP assurances, while the other two were conducted prior to the enactment of GLP. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies assessing toxicity following both oral and inhalation exposures. Oral studies evaluated both rats and mice while the inhalation study only utilized rats. None of the studies followed established protocols and they were conducted prior to the enactment of GLP. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them "reliable with restrictions".

Repeat Dose Toxicity - This endpoint is filled by data from an oral drinking water study of 10 - 13 months duration and an inhalation study of 17.5 weeks duration. Neither study followed established protocols and were conducted prior to the enactment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them "reliable with restrictions".

Genetic Toxicity
Mutation - This endpoint is filled with a single study in *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2*uvr*A). This study followed an established guideline (EEC Annex V Guideline number B.14 and B.13) and was conducted under GLP assurances.

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed an established OECD guideline (#473) and was conducted under GLP assurances.

Developmental
Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Reproductive
Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established guidelines, or utilized methods that were very similar and scientifically appropriate. Some studies were conducted under GLP assurances while some were conducted prior to its enactment. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MPK were all obtained from textbooks referenced within the HSDB. These data indicate that MPK is a liquid at room temperature with a relatively high vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual studies, acceptable estimation modeling programs, and a technical discussion. As a result of its relatively high solubility in water, fugacity estimations predict that MPK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone is not anticipated to under go hydrolysis. Results from the two biodegradation studies indicate that, under the conditions of these assays, MPK is considered to be "readily biodegradable" in the environment. Nevertheless, due to its primary use in coatings applications, releases into the environment will primarily occur through evaporative emissions where degradation in the atmosphere is expected. The predicted half-life though for this route of elimination ranged from 26 – 79 hours.

The toxic potential of MPK to aquatic organisms and algae were determined through well-conducted studies. The results of these studies demonstrate that fish and Dapnia are not sensitive species, with NOEC's >1000 mg/l. Whereas, the 72-hour E_bC_{50} and E_rC_{50} values for algal effects indicate that MPK would not be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in coatings applications. Furthermore, it is noted as being readily biodegradable following exposure to wastewater microbes.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The LD_{50} value noted in both rats and mice was between 1600-3200 mg/kg and an LC_{50} value of between 2000-4000 ppm following a 4-hour exposure. Repeat exposure data in rats following exposure durations of both 17.5 weeks (inhalation) and 10-13 months (through drinking water) indicate the material is tolerated quite well. The NOAEL in the 17.5- week study was 305 ppm (1,074 mg/m^3). This was the only concentration level examined in this study. In this study, there was no clinical signs or histological evidence of neurotoxicity exhibited at any exposure level. The only effect noted (seen in only one animal) in any of the tissues microscopically evaluated that was deemed to have been related to MPK exposure consisted of a very slight enlargement of hepatocytes. The NOAEL from the 10-month exposure study was 0.5% (250 mg/kg). In this study a slight decrease (maximum of 9% at Day 298) in body weight was seen at the highest dose (1.0%). There was no clinical or histological evidence of neurotoxicity exhibited by any of the treated animals in this study either. There was no effect on organ weights or lesions noted in any of the other many tissues microscopically evaluated. Results from mutagenicity and chromosomal aberration studies that utilized OECD guidelines and GLP assurances indicate this compound does not induce genotoxicity. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MPK is not likely to induce either type of effect at dose levels up to 5 mg/L. Evidence of maternal effects were noted at 2.5 mg/L and higher, and consisted primarily of decreases in activity level.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MPK that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (2) and the systematic approach described by Klimisch *et al.* (3). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 1.2, Syracuse Research Corporation, Syracuse, New York.

2. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

3. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

4. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.